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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
09/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,561	OI ET AL.	
	Examiner	Art Unit	
	BINTA M. ROBINSON	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 19-21* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/08;4/28/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner notes applicant's election of Group I, directed to claims 1-16, and 21. The applicant failed to elect a species in the response dated March 31, 2008 but however, did consent to a telephonic election detailed below.

Election/Restrictions

2. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

The compounds in claim 11 and the species of examples 1 -433 at pages 82-418 of the specification.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic: 1-10, 12-16, 19-21.

3. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The species lack a common core.

4. During a telephone conversation with Greg Butler on 8/27/08 a provisional election was made with traverse to elect the species of

methyl 3-({5-(aminomethyl)-6-isobutyl-2-methyl-4-(4-methylphenyl)pyridin-3-yl]methoxy)-1-methyl-1H-pyrazole-4-carboxylate, which is the second species from the top in claim 11. Affirmation of this election must be made by applicant in replying to this Office action. Claims 19-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

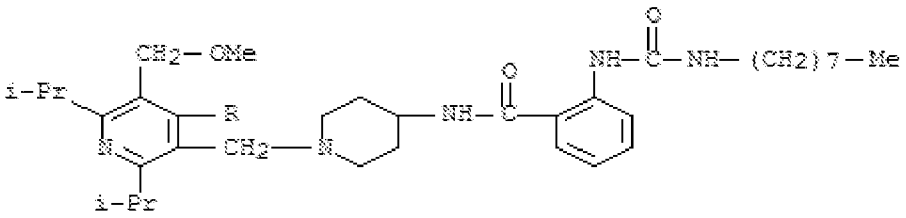
6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

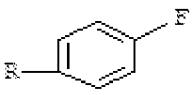
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-5, 7, 9, 12, 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Schoen et. al. the compounds of examples 69, 70 and 71. At column 159,

lines 1-15, column 160, lines 1-20, and at column 160, lines 35-55, see the compounds of examples 69-71 respectively.

8. Claims 1-5, 7, 9, 12, 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Hcaplus 1997:9205. Hcaplus 1997:9205 discloses the instant



compound, 

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9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

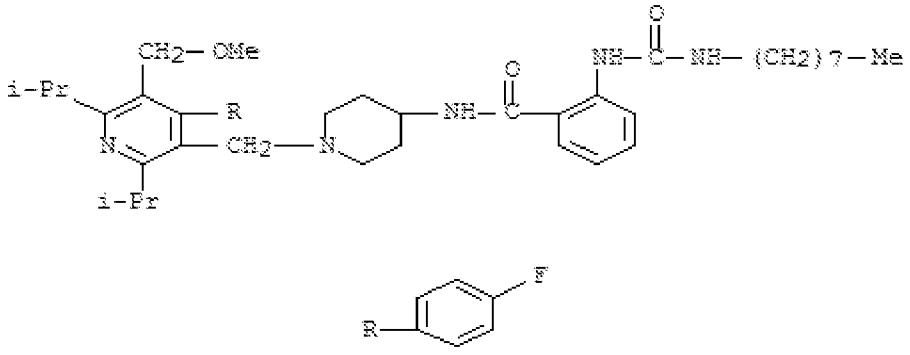
10. Claims 13-14 rejected under 35 U.S.C. 103(a) as being unpatentable over Schoen et. al.

11. Schoen et. al. teaches the instant compounds of examples 69, 70 and 71. At column 159, lines 1-15, column 160, lines 1-20, and at column 160, lines 35-55, see the compounds of examples 69-71 respectively.

. The difference between the prior art compounds and the claimed compositions is the teaching of a compound mixed with a pharmaceutically acceptable carrier in the instant application versus a compound that is taught in the prior art that is not mixed with a

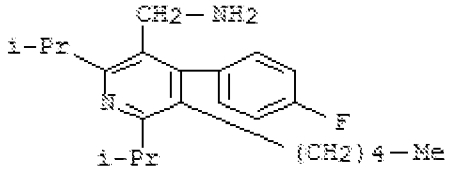
pharmaceutically acceptable carrier. It would have been obvious to one of ordinary skill in the art to make pharmaceutical compositions out of these compounds because it is obvious to place these compounds in ethanol or another, non-toxic solvent in which they are soluble, because they are soluble in ethanol or other non-toxic solvents. Accordingly, the compositions and process of making them are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compositions and process of making them over those of the prior art compounds.

Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hcaplus 1997:9205Hcaplus 1997:9205 teaches the instant compound,

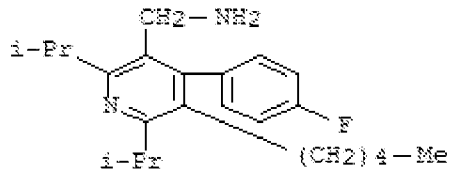


. The difference between the prior art compounds and the claimed compositions is the teaching of a compound mixed with a pharmaceutically acceptable carrier in the instant application versus a compound that is taught in the prior art that is not mixed with a pharmaceutically acceptable carrier. It would have been obvious to one of ordinary skill in the art to make pharmaceutical compositions out of these compounds because it is obvious to place these compounds in ethanol or another, non-toxic solvent in which they are soluble, because they are soluble in ethanol or other non-toxic solvents. Accordingly, the compositions and process of making them are deemed unpatentable

therefrom in the absence of a showing of unexpected results for the claimed compositions and process of making them over those of the prior art compounds.

Claims 1, 3-7, 12,15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable et. al. over Hcaplus 2001:278024 in view of Patani et. al. Hcaplus 2001:278024 teaches the compound, 

. The difference between the prior art compound and the instantly claimed compounds is the teaching of the X moiety as methyl in the prior art rather than hydrogen in the instant compounds. Methyl can be a bioisosteric replacement for hydrogen. See page 3152 of Patani et. al. The prior art compound and the instant compounds are bioisosteres of each other. Bioisosteres are defined as compounds that elicit similar biological activity because of their similar physicochemical properties. See page 3148 of Patani et. al. It would have been obvious to one of ordinary skill in the art to modify the prior compound which is a bioisostere of the instant compound and which has pharmaceutical use to obtain the instant compound. For instance, see the compound,



. Accordingly, the instant compounds are deemed unpatentable therefrom in the absence of a showing of unexpected chemical results for the claimed polymorphs over those of the bioisosteres.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I and Ia with R1 equal to isobutyl, neopentyl, Q equal to a bond, L and La equal to methylene, X and Xa equal to carboxy, R3 equal to optinally substituted phenyl, and R4 equal to NH2, does not reasonably provide enablement for using the compounds of formula I and Ia, with R1, Q, L, La, X, Xa, R3, and R4 equal to all other moieties claimed. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining if any particular claimed compounds of formula I or Ia with R1, Q, L, La, Xa, X, R3, and R4 equal to all other moieties claimed other than those noted to be enabled above, would be active would require synthesis of the substrate and subjecting it to testing with Applicants' dipeptidyl peptidase IV inhibitory activity assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 419-421, which merely states Applicants' intent to make and use such compounds. c) In the instant case none of the working examples contains any radicals R1, Q, L, La, Xa,X, R3, and R4 equal to moieties other than those noted to be enabled above.

d) The nature of the invention is inhibition of dipeptidyl dipeptidase -IV and treatment of human diseases with Applicants' compounds. This involves physiological activity. e) There is no reasonable basis for the assumption that the myriad of compounds embraced the present formulas (I) and Ia will all share the same biological properties. The diverse claimed radicals are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties

were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope

with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I) and Ia. Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds,

does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective.

Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found at page 51, lines 12-34, and at page 53, lines 1-10 c) There is no working example of a prodrug of a compound the formulas I. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical

chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formulas I, as well as the presently unknown list of potential prodrug derivatives embraced by claim 12.

The elected species is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (703) 306-5437. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone numbers for the organization where this application or proceeding is assigned are (703)308-7922 for regular communications and (703)308-7922 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0193.

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625

/Binta M Robinson/
Examiner, Art Unit 1625
September 4, 2008

13.